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Botulinum A Toxin Intravesical Injections in the Treatment of Refractory Overactive Bladder in Patients with Parkinson's Disease

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1. Introduction

In Parkinson's disease (PD) non-motor symptoms including urinary disorders have been recognized as important features of the disease (Emre, 2003; Hely et al., 2005; Mathias, 2002; Pfeiffer, 2003; Rojo et al., 2003; Senard et al., 1997; Winge et al., 2003; Lang & Obeso, 2004). In this chapter we will review the clinical features, the pathophysiology and the treatment of urinary disturbances in PD. We will also discuss recent data on the use of intradetrusorial botulinum A toxin injections (BoNT/A) (Giannantoni et al., 2009; Giannantoni et al., 2011).

2. Parkinson's disease and neurogenic bladder

2.1 Prevalence of urinary symptoms

Earlier studies suggested that the prevalence of urinary symptoms in patients with PD ranges from 38% to 71% (Andersen 1985; Berger et al., 1987; Hald & We, 1982; Hattori et al., 1992; Porter et al., 1971) however in a number of these studies the clinical distinction between PD and other parkinsonisms, including multiple-system atrophy (MSA) was not addressed. Furthermore, some studies were based on patients presenting to urology clinics with urinary symptoms. (Berger et al., 1987; Hattori et al., 1992; Pavlakis et al., 1983). More recent studies in PD using validated questionnaires showed that the prevalence of urinary symptoms varied between 27% (Araki & Kuno, 2000a) to 39% (Campos-Sousa et al., 2003) and using a non validated questionnaire was greater than 40% (Sakakibara et al., 2001). Additionally Araki and Kuno (2000a) found a correlation between urinary disturbances and neurological disability and between severity of urinary disturbances and stages of the disease (Sakakibara et al., 2001), suggesting a relationship between dopaminergic degeneration and voiding dysfunction (Sakakibara et al., 2001).

2.2 Clinical features of urinary symptoms

Nocturia is the most prevalent lower urinary tract symptom (LUTS) reported by PD patients (>60%) (Campos-Sousa et al., 2003). Patients complain also of urgency (33%-54%)

(Araki & Kuno, 2000a; Campos Sousa et al., 2003) and frequency (16%–36%) (Araki & Kuno, 2000a; Campos Sousa et al., 2003), and urge urinary incontinence, particularly if poor mobility complicates their bladder disorder (Araki & Kuno 2000a; Campos Sousa et al., 2003; Lemack et al., 2000). Men with PD often have a coexisting benign prostatic hyperplasia worsening detrusor overactivity. In female patients overactive (urgency, frequency, urge incontinence) and obstructive (hesitancy, poor flow, dribbling) symptoms may also coexist. Evidence of bladder dysfunction in genetically determined Parkinsonism is controversial. In one study at least three cases of PARK1 α -synuclein-positive individuals were incontinent (Spira et al., 2001), while in another none of 17 patients with autosomal-recessive-type juvenile PD had bladder dysfunction (Ishikawa & Tsuji, 1996).

2.3 Neurogenic causes of bladder symptoms and voiding dysfunction in PD

There are several neurogenic causes of bladder symptoms in PD. Some Authors have suggested that an impaired relaxation or bradykinesia of the urethral sphincter can result in voiding dysfunction (Christmas et al., 1988; Galloway 1983) due to bladder outflow obstruction and, therefore, to detrusor overactivity. Studies using cystometry, however, have shown that obstructive voiding patterns are not common in PD patients (Araki et al., 2000b; Dmochowski, 1999) indicating that other mechanisms play a significant role.

3. Normal nervous control of the micturition reflex

Urinary storing and micturition rely on the interplay of a number of neural structures in the brain, spinal cord and peripheral ganglia. The complex relationship between central and peripheral pathways makes lower urinary tract (LUT) susceptible to a variety of neurologic disorders.

3.1 The role of Central Nervous System (CNS) in the control of the micturition reflex

The normal micturition reflex in the adult is mediated by a spino-bulbo-spinal pathway, which passes through relay centers in the brain. Micturition occurs in response to afferent signals from the lower urinary tract, and the distension of the bladder wall is considered the primary stimulus (de Groat et al., 1999; de Groat & Yoshimura, 2001).

During bladder filling, once threshold tension is achieved, afferent impulses, conveyed mainly by the pelvic nerve, reach the CNS. Afferent neurons send information to the periaqueductal gray, and relay with the pontine tegmentum, where two different regions involved in micturition control have been described acting independently (Blok & Holstege, 1999a, Griffiths et al., 1990). One is a dorsomedially located M-region, corresponding to Barrington's nucleus or the pontine micturition center (PMC). A more laterally located L-region may serve as a pontine urine storage center, and likely suppress bladder contraction by regulating the activity of the striated musculature of the bladder outlet during urine storage. Centers rostral to the pons control the beginning of micturition. The forebrain, therefore, even though not essential for the basic micturition reflex plays a role in determining when and where micturition should take place (Blok & Holstege, 1999b). Recent positron emission tomography studies gave further information on the brain structures involved in urine storage and voiding (Athwal et al., 2001; Blok et al., 1997; Matsuura et al., 2002; Nour et al., 2000).

3.2 Neurotransmitters mainly involved in voiding dysfunction due to Parkinson's disease

The micturition reflexes use several transmitter systems that may be targets for drugs aimed at control of micturition. Among these, dopamine and GABA pathways are fully involved in the control of micturition reflex and depletion of dopamine and GABA has been observed in Parkinson's disease.

3.2.1 Dopamine

Central dopaminergic pathways can have both facilitatory and inhibitory effects on micturition by actions on D1-like (D1 or D5) and D2-like (D2, D3, or D4) dopaminergic receptors. Patients with PD often have neurogenic detrusor over activity and voiding dysfunction (Berger et al., 1987), possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory D1-like receptors (Yoshimura et al., 1993). Micturition, however, can be activated via D2-like receptors involving brainstem and spinal cord circuits. Microinjection of dopamine into the pontine micturition center reduced bladder capacity and facilitated the micturition reflex in cats (de Groat et al., 1993). Apomorphine, which stimulates both D1- and D2-like receptors, induced bladder overactivity in anesthetized rats (Sillén et al., 1981). In female rats, the role of dopamine D1 and D2 receptors in the volume induced micturition reflex, was investigated cystometrically (Seki et al., 2001) and the results, which are in agreement with previously data (de Groat & Yoshimura, 2001), suggested that D1 receptors tonically inhibit and D2 receptors facilitate the micturition reflex. In conclusion central dopaminergic pathways exhibit different effects on micturition via multiple receptors at different sites in the central nervous system.

3.2.2 GABA

GABA pathways are also involved in voiding dysfunction due to Parkinson's disease. GABA (γ -amino butyric acid) has been identified as an inhibitory transmitter at both spinal and supraspinal synapses in the mammalian CNS. At least in some species, the supraspinal micturition reflex pathway is under a tonic GABAergic inhibitory control (de Groat et al., 1993, 1999). GABA functions appear to be triggered by binding of GABA to its ionotropic receptors, GABA-A and GABA-C, which are ligand-gated chloride channels, and its metabotropic receptor, GABA-B (Chebib & Johnston, 1999). Since blockade of GABA-A and GABA-B receptors in the spinal cord (Igawa et al., 1993; Pehrson et al., 2002) and brain (Maggi et al., 1987; Pehrson et al., 2002) stimulated rat micturition, an endogenous activation of GABA-A and GABA-B receptors may be responsible for continuous inhibition of the micturition reflex within the CNS. In the spinal cord, GABA-A receptors are more numerous than GABA-B receptors, except for the dorsal horn where GABA-B receptors predominate (Malcangio and Bowery, 1996; Coggeshall and Carlton, 1997). It is well known that stimulation of the PMC results in an immediate relaxation of the external striated sphincter and a contraction of the detrusor muscle of the bladder. Blok et al. (Block et al., 1997) demonstrated in cats a direct pathway from the PMC to the dorsal gray commissure of the sacral cord. It was suggested that the pathway produced relaxation of the external striated sphincter during micturition via GABA-mediated inhibitory modulation on the urethral sphincter motoneurons in the Onuf nucleus.

4. The pathophysiology of voiding dysfunction in Parkinson's disease

The hypothesis most widely accepted is that in healthy individuals basal ganglia output has an overall inhibitory effect on the micturition reflex. In PD animal models depletion of dopaminergic neurones induces overactive bladder, (Yoshimura et al., 1993, 1998, 2003) and D1 receptor agonists produce inhibition of the micturition reflex in a dose-dependent manner while D2 receptor stimulation facilitates micturition. In PD degeneration of dopaminergic neurons in the substantia nigra leads to detrusor hyperactivity, through an inability to activate the D1-mediated tonic inhibition. A parallel mechanism may be that in PD, the inhibitory dopaminergic neurons originating in the substantia nigra may be more damaged than the excitatory dopaminergic neurons originating in the VTA, thereby inducing urgency and frequency.

Patients with PD and bladder symptoms have less uptake of [123I]-2 β -carbomethoxy-3 β -(4-iodophenyl) tropane (β -CIT) in the striatum than patients with PD but without bladder dysfunction, indicating a correlation between urinary dysfunction and degeneration of the nigrostriatal dopaminergic cells (Sakakibara et al., 2001). Winge and colleagues (Winge et al., 2005) recently demonstrated that the presence of bladder symptoms correlate with the decrease in the total number of dopaminergic neurones in the striatum and that the degeneration of the caudate correlates with severity of bladder symptoms. It is also possible that anti-parkinsonian medications may affect bladder function, but the results on the effects of levodopa or apomorphine are controversial. In one study, detrusor overactivity improved after administration of apomorphine and, to a lesser extent, after levodopa (Aranda & Cramer, 1993), but in patients showing on-off phenomena, detrusor overactivity improved with levodopa in some patients and worsened in others (Fitzmaurice et al., 1985). A recent study suggested that in advanced PD, levodopa exacerbates detrusor overactivity in the filling phase, but also improves bladder emptying through increased detrusor contractility (Uchiyama et al., 2003). The unpredictable effect of medication is not related to stage of disease, age, or whether the patient had symptoms of bladder dysfunction (Winge et al., 2002). In the study of Winge and colleagues (Winge et al., 2004), the authors suggested that the effects of medication are mediated through cortical mechanisms, as the ability to separate and integrate sensory input measured using urodynamics is influenced by medication.

5. Management of urinary symptoms in Parkinson's Disease

Questionnaires including "bother" scores identify LUTS in PD with higher specificity than questionnaires without "bother" scores (Winge et al., 2003). When addressing bladder problems in patients with Parkinsonism in daily clinical work, systematic interview is needed. Addressing nocturia, urgency, frequency feeling of incomplete emptying and (urge) incontinence often provides the needed information for initiating treatment. It is important to address how these symptoms affect the daily life of the patients, as symptoms of overactive bladder may be particularly unpleasant in a patient with an akinetic rigid syndrome with postural instability.

Neurogenic bladder symptoms are generally treated with anticholinergics (Andersson, 2000; Appell, 1997) including oxybutynin chloride, tolterodine tartrate, and trospium chloride and possibly also solifenacin. No placebo control double-blind or randomized studies, however, have been performed in PD. Anticholinergics can be used in PD patients with urgency and

frequency since they reduce the parasympathetic effect on the bladder. Patients generally tolerate anticholinergic drugs and benefit from their use. A study in patients without neurological diseases showed that the extended release tolterodine produces less side effects than oxybutinin (Sussman & Garely, 2002; Todorova et al., 2001). Anticholinergics usually provide only modest clinical improvement and in more than 60% of treated patients they induce adverse effects such as dry mouth and constipation (Di Stasi, 2001; Winge & Fowler, 2006). Another disadvantage is that anticholinergics may induce or worsen cognitive impairment (Kay & Ebinger, 2008; Winge & Fowler, 2006). There are no studies, however, addressing the issue of possible worsening of cognitive impairment using anticholinergics in patients with PD.

6. Botulinum A toxin as second line treatment for refractory detrusor over activity and over active bladder symptoms

To date when urinary incontinence persists and patients become severely disabled a long-term indwelling catheter remains the only option for avoiding urinary incontinence. Botulinum A toxin has been successfully introduced for the treatment of intractable detrusor overactivity (Schurch et al., 2000) and it is now widely used for a number of neurological conditions characterized by muscle hyperactivity (Jankovic, 2004; Ward et al., 2006). Intravesical injections of BoNT/A provide satisfactory long-term results, and are now considered as second line-therapy in neurogenic patients who do not respond to standard anticholinergics. The use of botulinum neurotoxins in the lower urinary tract (LUT) was pioneered as early as 20 yr ago with injections into the urethral sphincter (Dykstra et al., 1988) reducing bladder-voiding pressures, urethral pressures, and post void residual (PVR) urine.

BoNT/A consists of a light chain attached to a heavy chain via a disulfide bond with an associated zinc atom. It is synthesised as a single-chain polypeptide with a molecular weight of 150 kDa, which is then cleft into its active dichain polypeptide form. The heavy chain (about 100 kDa) allows for binding to the neuron and internalisation of the toxin, whereas the light chain (about 50 kDa) actively cleaves SNAP25 (synaptosomal-associated protein with a molecular weight 25 kDa) on the protein complex that is responsible for docking and releasing vesicles containing neurotransmitters (Dolly, 2003).

In neurogenic detrusor overactivity as well as in patients with idiopathic detrusor overactivity, the post-treatment reduction in detrusor pressures during both phasic involuntary contractions and on voiding (Popat et al., 2005; Reitz et al., 2004; Schurch et al., 2005) suggests an effect of BoNT/A on the motor innervation of the detrusor, although the neurological deficit which additionally affects voiding efficiency in the NDO group may partly explain the high rate of posttreatment clean intermittent self-catheterisations (CISC). Patients, however, also report a rapid reduction in their sensations of urgency, which are associated with involuntary detrusor overactivity (Rapp et al., 2004; Schmid et al., 2006). Although the exact nature and cause of urgency remains to be elucidated, abnormal afferent activity is thought to be a significant cause of spinal NDO (Yoshimura, 1999), and much less is known about the role of afferents in IDO. In both neural and bladder tissue, BoNT/A affected the release of numerous sensory transmitters other than ACh, including adenosine triphosphate (ATP), substance P, calcitonin gene related peptide (CGRP), and glutamate. BoNT/A may also interfere with vesicle trafficking (Apostolidis et al., 2006), expression of sensory receptors (Apostolidis et al., 2005) and nerve growth factor (NGF) in the bladder

wall (Giannantoni et al., 2006). It is therefore likely that in addition to a direct effect on detrusor motor innervation, BoNT/A also modulates intrinsic bladder reflexes through a multimodal effect on sensory pathways.

In neurogenic patients it has been demonstrated that BoNT/A decrease symptoms of neurogenic detrusor overactivity. The majority of treated patients had spinal neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis. Despite heterogeneous designs, almost all single-injection published studies showed significant improvements in outcomes measures including frequency of incontinence episodes, maximum cystometric capacity and maximum detrusor pressure. In spinal NDO patients the mean percentage of those who became fully continent was 56.6% (range: 30–87%) whereas the rate of full return to continence was only 8% in patients with NDO due to cerebrovascular accident. After a rapid onset of effect (Kalsi et al., 2008), the mean duration of efficacy in single-injection studies was 8 months (range: 12–36 wk). Repeated treatments showed sustained clinical benefits in open-label studies using up to five injections of Botox or seven injections of Dysport (Del Popolo et al., 2008; Grosse et al., 2005; Karsenty et al., 2006; Reitz et al., 2007).

7. Botulinum A toxin in the treatment of refractory detrusor overactivity and overactive bladder symptoms due to Parkinson's disease

Since 2000 we have been using BoNT/A as second line therapy for refractory overactive bladder symptoms and detrusor overactivity (DO) of both neurogenic and non-neurogenic origin. Here we review the results of our open label, prospective, non randomized study on the use of BoNT/A in patients with Parkinson's disease affected by intractable overactive bladder (OAB) symptoms and DO (Giannantoni et al., 2009, Giannatoni et al., 2011).

7.1 Patients and methods

Seventeen patients diagnosed with PD according to United Kingdom Brain Bank criteria and affected by overactive bladder symptoms and DO were enrolled in a prospective study. They were all refractory to standard anticholinergic therapy. Disease severity was assessed with the Unified Parkinson's Disease Rating Scale and Hoehn-Yahr stages 1 to 5. All patients had moderate-severe disability. Patients were studied while they were on their usual drug regimens for PD. Exclusion criteria were urogenital prolapsed in females, bladder outlet obstruction due to benign prostatic hyperplasia in men and recurrent urinary tract infections. No patients were on anticoagulant therapy or drugs interfering with neuromuscular transmission. The study was approved by the local ethics committee and patients provided informed consent. Patients unwilling or unable to perform intermittent catheterization, were excluded from the study. We used 150 ml as a cutoff residual volume for starting intermittent bladder catheterization.

7.2 Preliminary urological assessment

History, physical examination, serum laboratory tests, urinalysis, urine culture and urinary tract imaging by ultrasound were performed before commencing the study. The daily frequency of urinary symptoms was assessed with a voiding diary that patients completed for 30 days before the study. Patients were also asked to complete a standardized QoL questionnaire on urinary incontinence (I-QoL). Patients underwent urodynamics, including pressure flow studies and the recording of the electromyographic activity of pelvic floor muscle and external urethral sphincter, according to International Continence Society

Standards. During cystometry first volume and maximum pressure of uninhibited detrusor contractions (UDC) and maximum cystometric capacity were recorded. On pressure flow study detrusor pressure at maximum flow rate (pDetQmax), maximum flow rate (Qmax) and postvoid residual volume were monitored. All patients received a single treatment with BoNT/A (Botox, Allergan, Irvine-CA, USA) diluted in normal saline injected into the detrusor muscle. The trigone, the posterior and lateral walls of the bladder have been injected during cystoscopy, under short lasting general anaesthesia. Six out of the seventeen patients received 200 UI of BoNT/A, whereas eleven of the seventeen PD patients received 100 UI of BoNT/A. Primary outcome measures were: changes in day-time and night-time urinary frequency and frequency of daily urinary incontinence episodes and in I-QoL questionnaire; secondary outcomes were changes on the impact of urinary symptoms in daily life activities was evaluated with VAS scores and in urodynamic parameters. Clinical, urodynamic and I-QoL and VAS were performed before, one, three and six months after BoNT/A injection. Urinalysis and culture were performed also at the same time intervals.

7.3 Statistical analysis

Friedman's repeated measures ANOVA was used to evaluate changes in the clinical scores and urodynamic findings of PD patients. Wilcoxon's test was performed for the post-hoc analysis. Pearson's correlation coefficient was also applied and Holm's correction for multiple comparisons was used to disclose false significance. $P < 0.05$ was considered to indicate statistical significance.

7.4 Clinical results

Before treatment all seventeen patients complained of increased daytime (9.29 ± 0.3 episodes/day) and night-time urinary frequency (4.11 ± 0.6 episodes/night) and daily episodes of urinary incontinence (5.05 ± 0.2 episodes/day). They also had urgency and low I-QoL scores (22.8 ± 2) and VAS scores (3.3 ± 0.1). After BoNT/A treatment daytime and night-time urinary frequency and the number of daily episodes of urinary incontinence were significantly reduced (daytime urinary frequency: $p < 0.0001$; night-time urinary frequency: $p = 0.002$; daily urinary incontinence episodes: $p = 0.001$) (Fig.1) at one, three and six months follow up. Six out seventeen patients achieved a complete urinary continence at one and 3-mos follow up. After BoNT/A treatment there was also a significant improvement in the I-QoL and VAS scores after BoNT/A (I-QoL: $p < 0.0001$; VAS: $p < 0.0002$) at one, three and six months. Finally, we did not find any significant difference between the improvement observed in daytime and night-time urinary frequency, in the number of episodes of daily urinary incontinence and in the I-QoL and VAS scores in PD patients who received 100 UI with that obtained in patients treated with 200 UI of BoNT/A ($p > 0.05$). Clinical results are showed in Fig.1.

7.5 Urodynamic results

Baseline: all the patients showed detrusor overactivity; mean values of UDC-first volume UDC-p max and maximum cystometric capacity were 219 ± 20 ml, 30 ± 2 cmH₂O and 265 ± 16 ml, respectively. On pressure-flow studies, mean values of pDetQmax and Qmax were 22.3 ± 2 cmH₂O and 18.3 ± 1.5 ml/sec, respectively. All patients completely emptied their bladders. After BoNT/A treatment, we observed a significant decrease in the first volume and the maximum pressure of uninhibited detrusor contractions and a significant increase in

maximum cystometric capacity at one, three and six months after treatment. Changes in these parameters were similar in both groups of PD patients (Fig.2). With regards to post-void residual volume, it was similar in PD patients receiving 100 and 200 UI of BoNT/A at one month, whereas it returned to baseline values only in PD patients receiving 100 UI at three and six months after BoNT/A injection. Overall, three patients needed to perform intermittent catheterization twice daily for 3 months due to a high increase in post void residual volume after BoNT/A injection.

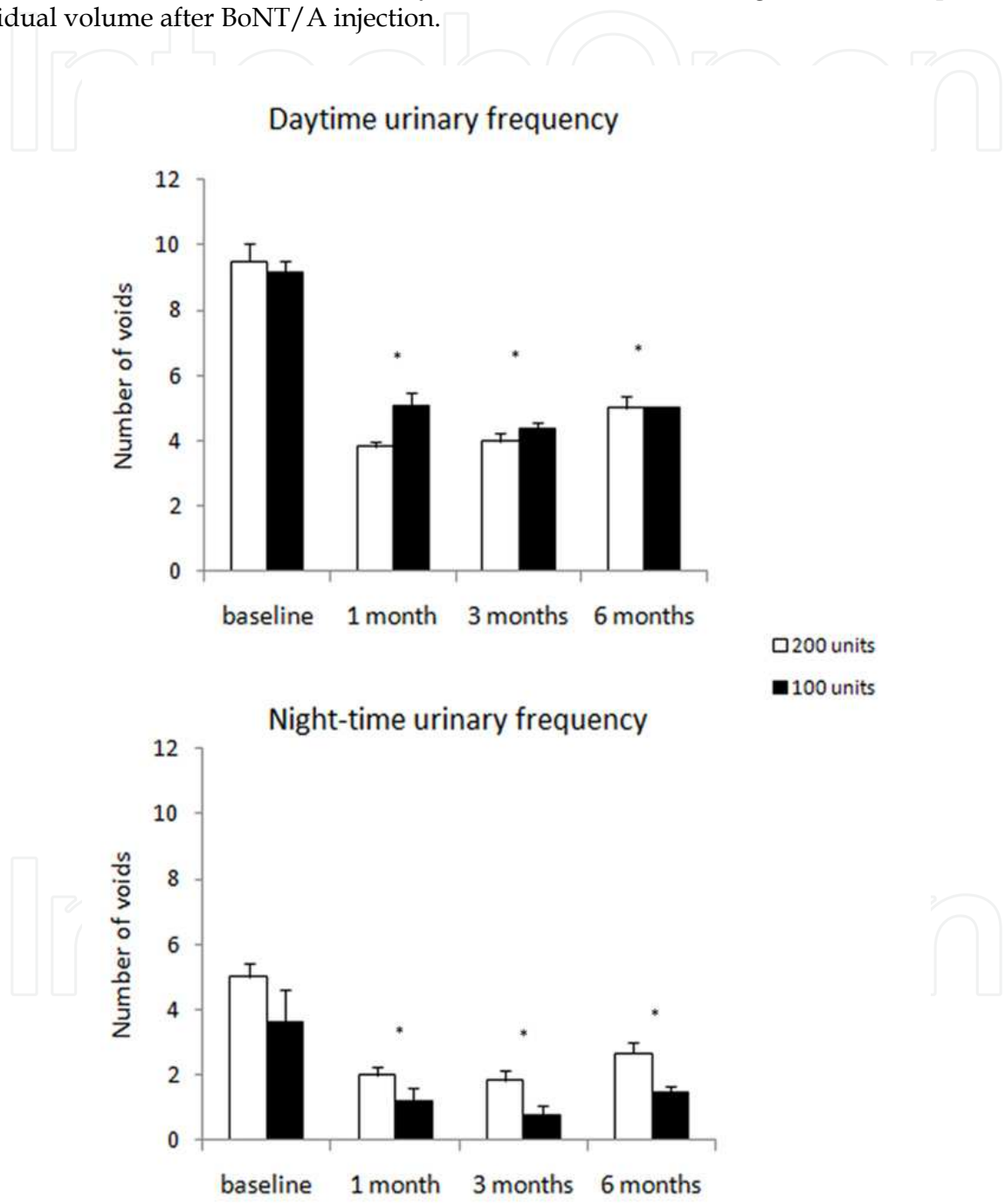


Fig. 1. Daytime urinary frequency (upper panel) and night-time urinary frequency (lower panel) in patients with Parkinson's disease at baseline, one, three and six months after BoNT/A injection. Open bars represent mean data \pm SE in patients injected with 200 units, closed bars data in patients injected with 100 units. Asterisks indicate statistical significance

Maximum cystometric capacity and post-void residual volume

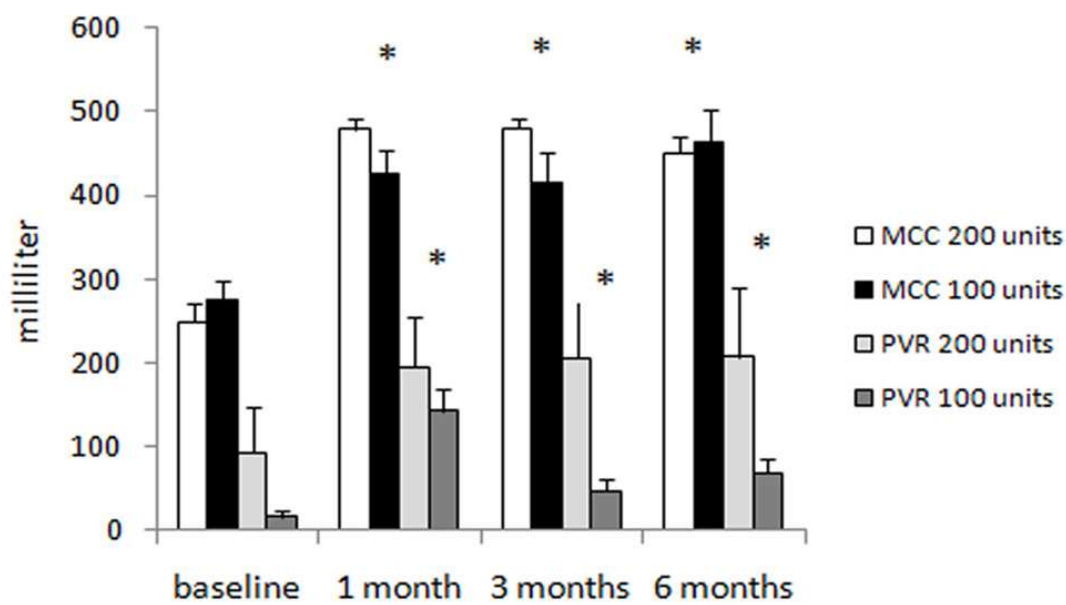


Fig. 2. Maximum cystometric capacity and post-void residual volume in patients with Parkinson's disease at baseline, one, three and six months after BoNT/A injection. Each bar represents mean data ±SE in patients injected with 200 units and 100 units. Asterisks indicate statistical significance.

7.6 Correlations between clinical and urodynamic variables

Changes in the I-QoL significantly correlated with daytime urinary frequency ($r=-0.69$, $p=0.002$) in all the PD patients.

7.7 Discussion

In our PD patients, BoNT/A intradetrusorial injection induced a significant reduction in daytime and night-time urinary frequency and in the frequency of urinary incontinence, an increase in the quality of life scores and a significant amelioration in urodynamic parameters. The follow-up assessment extends our previous findings at three months (Giannantoni et al., 2009) by showing that the BoNT/A-induced clinical and urodynamic improvement lasts at least six months (Giannantoni et al., 2011). We also noted that clinical and urodynamic amelioration was similar when comparing patients treated with 100 UI of BoNT/A with those treated with 200 UI. Worth of noting, incomplete voiding symptoms were unrelated to the BoNT/A dosage used. Also patients with multiple sclerosis treated with 100 Units and patients with idiopathic overactive bladder treated with 200 and 300 units of BoNT/A showed an increase in post-void residual volume (Flynn et al., 2009; Mehnert et al., 2010; Sahai et al., 2009). Our results on post-void residual volume are in contrast with those reported by Kulaksizoglu and Parman (Kulaksizoglu & Parman, 2010) who treated parkinsonian patients with Dysport 500 Units. In their series none of the patients studied needed intermittent catheterization. Despite of the presence of post-void residual volume in our PD patients, we did not observe a significant reduction in other parameters accounting for detrusor muscle strength (PdetQmax, Qmax). It is well known

that BoNT/A induces striated muscle denervation and weakness lasting about 3-4 months (Hamjian et al., 1994; Schiavo et al., 1994). In striated muscle it has been observed that the neurotoxin not only modulates extra-fusal component but also influences the altered muscle spindle afferent input (Abbruzzese et al., 2006; Currà & Berardelli, 2009; Rosales & Dressler, 2010; Trompetto et al., 2008). In detrusor smooth muscle the effects of BoNT/A injection last longer than in striated muscle. In vitro and in vivo experimental studies suggest that the long-lasting effect of the BoNT/A injection in the detrusor muscle could be attributed to the lack of axonal sprouting, as observed in detrusor biopsies after toxin injection (Haferkamp et al., 2004). Studies on biopsies from patients with neurogenic overactive bladder who receive an intradetrusor BoNT/A injection (Apostolidis et al., 2006; Giannantoni et al., 2006), however, have shown decreased levels of sensory receptors P2X3, TRPV1 and NGF, thereby suggesting that BoNT/A may act by reducing the afferent nervous transmission.

7.8 Conclusions

PD patients with OAB symptoms and detrusor overactivity refractory to standard treatments can be successfully treated with intravesical injections of BoNT/A. Low doses (100 U BoNT/A) induces similar clinical and urodynamic efficacy as higher doses of the neurotoxin. The reported increase in post void residual volume is present only in some patients and lasts for a limited time. Low doses of BoNT/A can be used as second-line treatment for OAB symptoms and DO also in patients with PD.

8. References

- Abbruzzese, G. & Berardelli, A.(2006). Neurophysiological effects of botulinum toxin type A. *Neurotox Res*, Vol. 9, pp. 109-114.
- Andersen, JT. (1985). Disturbances of bladder and urethral function in Parkinson's disease. *Int Urol Nephrol*, Vol. 17, pp. 35- 41.
- Andersson, KE. (2000). Treatment of overactive bladder: other drug mechanisms. *Urology*, Vol. 55, pp. 51-57.
- Andersson, KE. (2002). Bladder activation: afferent mechanisms. *Urology*, Vol. 59, Suppl. 1, pp. 43-50.
- Apostolidis, A.; Popat, R.; Yiangou, Y., Cockayne, D.; Ford, A.P.; Davis, J.B.; Dasgupta; P.; Fowler, J.C. & Anand, P. (2005). Decreased sensory receptors P2x3 and Trpv1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol*, Vol. 174, pp. 977-83.
- Apostolidis, A.; Dasgupta, P. & Fowler, C.J. (2006). Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol*, Vol 49, pp.644-50.
- Appell, R.A. (1997). Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology*, Vol 50, pp. 90- 96.
- Araki, I. & Kuno, S. (2000a). Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. *J Neurol Neurosurg Psychiatry*, Vol 68, pp. 429-433.
- Araki, I.; Kitahara, M.; Oida, T. & Kuno, S. (2000b). Voiding dysfunction and parkinson's disease: urodynamic abnormalities and urinary symptoms. *J Urol*, Vol 164, pp. 1640 -1643.

- Aranda, B.; Perrigot, M.; Mazieres, L. & Pierrot-Deseilligny, E. (1983). Bladder sphincter disorders in Parkinson's disease. *Rev Neurol*, Vol 139, pp. 283-288.
- Aranda, B. & Cramer, P. (1993). Effects of apomorphine and L-dopa on the parkinsonian bladder. *Neurourol Urodyn*, Vol 12, pp. 203-209.
- Athwal, B.S.; Berkley, K.J.; Hussain, I.; Brennan, A.; Craggs, M.; Sakakibara, R., Frackowiak, R.S. & Fowler, C.J. (2001). Brain responses to changes in bladder volume and urge to void in healthy men. *Brain*, Vol 124, pp. 369-377.
- Berger, Y.; Blaivas, J.G.; DeLaRocha, E.R. & Salinas, J.M. (1987). Urodynamic findings in Parkinson's disease. *J Urol*, Vol 138, pp. 836-838.
- Birder, L.A. & De Groat, W.C. (1992) The effect of glutamate antagonists on c-fos expression induced in spinal neurons by irritation of the lower urinary tract. *Brain Res*, Vol 580, pp. 115-120.
- Blok, B.F. & Holstege, G. (1999) Two pontine micturition centers in the cat are not interconnected directly: implications for the central organization of micturition. *J Comp Neurol*, Vol 403, pp. 209-218.
- Blok, B.F. & Holstege, G. (1999b) The central control of micturition and continence: implications for urology. *BJU Int*, Vol 83, Suppl 2, pp. 1-6
- Blok, B.F., De Weerd H. & Holstege, G. (1997a). The pontine micturition centre projects to sacral cord GABA immunoreactive neurons in the cat. *Neurosci Lett*, Vol 233, pp. 109-112.
- Blok, B.F., Willemsen, A.T., & Holstege, G. (1997b). A PET study on brain control of micturition in humans. *Brain*, Vol 120, pp. 111-121.
- Campos-Sousa, R.N.; Quagliato, E.; Da Silva, B.B.; De CR, J.R.; Ribeiro, S.C. & De Carvalho, D.F. (2003). Urinary symptoms in Parkinson's disease: prevalence and associated factors. *Arq Neuropsiquiatr*, Vol 61, pp. 359-363.
- Chebib, M. & Johnston, G.A.R. (1999). The 'ABC' of GABA receptors: a brief review. *Clin Exp Pharmacol Physiol*, Vol 26, pp. 937-940.
- Christmas, T.J.; Kempster, P.A.; Chapple, C.R.; Frankel, J.P.; Lees, A.J.; Stern, G.M. & Milroy, E.J. (1988). Role of subcutaneous apomorphine in parkinsonian voiding dysfunction. *Lancet*, Vol 2, pp. 1451-1453.
- Coggeshall, R.E. & Carlton, S.M. (1997). Receptor localization in the mammalian dorsal horn and primary afferent neurons. *Brain Res Brain Res Rev*, Vol 24, pp. 28-66.
- Currà, A. & Berardelli, A. (2009). Do the unintended actions of botulinum toxin at distant sites have clinical implications? *Neurology*, Vol 72, pp. 1095-9.
- de Groat, W.C. & Yoshimura, N. (2001). Pharmacology of the lower urinary tract. *Annu Rev Pharmacol Toxicol*, Vol 41, pp. 691-721.
- Del Popolo, G.; Filocamo M.T.; Li Marzi, V.; Macchiarella, A.; Cecconi, F.; Lombardi, G. & Nicita, G. (2008). Neurogenic detrusor overactivity treated with English botulinum toxin A: 8-year experience of one single centre. *Eur Urol*, Vol. 53, pp. 1013-1020.
- Di Stasi, S.M.; Giannantoni, A.; Vespasiani, G.; Navarra, P.; Capelli, G.; Massoud, R. & Stephen, R.L. (2001). Intravesical electromotive administration of oxybutynin in patients with detrusor hyperreflexia unresponsive to standard anticholinergic regimens. *J Urol*, Vol 165, pp. 491-498
- Dmochowski, R.R. (1999) Female voiding dysfunction and movement disorders. *Int Urogynecol J Pelvic Floor Dysfunct* Vol 10, pp. 144-151.

- Dolly, O. (2003). Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. *Headache*, Vol 43, Suppl. 1, pp. 16-24.
- Dykstra, D.D.; Sidi, A.A.; Scott, A.B.; Pagel, J.M. & Goldish, G.D.(1988). Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol*, Vol 139, pp.919-922.
- Emre, M.(2003). Dementia associated with Parkinson's disease. *Lancet Neurol* Vol 2, pp. 229-237.
- Fitzmaurice, H.; Fowler, C.J.; Rickards, D.; Kirby, R.S. ; Quinn, N.P. ; Marsden, C.D. ; Milroy, E.J. & Turner-Warwick, R.T. (1985). Micturition disturbance in Parkinson's disease. *Br J Urol*, Vol 57, pp. 652- 656.
- Fowler, C.J.(2007) Update of the neurology of Parkinson's disease. *Neurourol Urodyn*, Vol 26, pp.103-109.
- Flynn, M.K.; Amundsen, C.L.; Perevich, M.; Liu, F. & Webster, G.D. (2009). Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. *J Urol*, Vol. 181, pp. 2608-2615.
- Gray, R.; Stern, G.& Malone-Lee, J. (1995). Lower urinary tract dysfunction in Parkinson's disease: changes relate to age and not disease. *Age Ageing*, Vol. 24, pp.499 -504.
- Galloway NT. (1983). Urethral sphincter abnormalities in parkinsonism. *Br J Urol*, Vol. 55, pp. 691- 693.
- Griffiths, D.; Holstege, G.; Dalm, X. & De Wall, H. (1990). Control and coordination of bladder and urethral function in the brainstem of the cat. *Neurourol Urodyn*, Vol. 9, pp.63-82.
- Giannantoni, A.; Di Stasi, S.M.; Nardicchi, V.; Zucchi, A.; Macchioni, L.; Bini, V.; Goracci, G.& Porena, M.(2006). Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. *J Urol*, Vol. 175, pp. 2341-2344.
- Giannantoni, A.; Rossi, A.; Mearini, E.; Del Zingaro, M.; Porena, M. & Berardelli, A. (2009). Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. *J Urol*, Vol.182, pp. 1453-1457.
- Giannantoni, A.; Conte, A.; Proietti, S.; Giovannozzi, S.; Rossi, A.; Fabbrini, G.; Porena, M. & Berardelli, A. (2011) Botulinum Toxin Type A in Patients With Parkinson's Disease and Refractory Overactive Bladder. *J Urol*, 2011 Jul 24 [Epub ahead of print]
- Grosse, J.; Kramer, G. & Stöhrer, M. (2005). Success of repeat detrusor injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. *Eur Urol*, Vol. 47, pp. 653-659.
- Haferkamp, A.; Schurch, B.; Reitz, A.; Krengel, U.; Grosse, J.; Kramer, G.; Schumacher, S.; Bastian, P.J.; Büttner, R. & Müller, S.C. (2004). Lack of ultrastructural detrusor changes following endoscopic injection of botulinum toxin type A in overactive neurogenic bladder. *Eur Urol*, Vol. 46, 784-791.
- Hald, T. & WE, B. (1982). *The urinary bladder, neurology and dynamics*. Baltimore, MD: Williams and Wilkins
- Hattori, T.; Yasuda, K.; Kita, K.& Hirayama, K. (1992). Voiding dysfunction in Parkinson's disease. *Jpn J Psychiatry Neurol*, Vol. 46, pp. 181-186.

- Hamjian, J.A. & Walker, F.O. (1994) Serial neurophysiological studies of intramuscular botulinum-A toxin in humans. *Muscle Nerve*, Vol. 17, pp. 1385-1392.
- Hely, M.A.; Morris, J.G.; Reid, W.G. & Trafficante, R. (2005). Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord*, Vol. 20, pp. 190-199.
- Hughes, A.J.; Daniel, S.E.; Kilford, L. & Lees, A.J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*, Vol. 55, pp. 181-184.
- Igawa, Y.; Mattiasson, A. & Andersson, K.E. (1993). Effects of GABA-receptor stimulation and blockade on micturition in normal rats and rats with bladder outflow obstruction. *J Urol*, Vol. 150, pp. 537-542.
- Ishikawa, A. & Tsuji, S. (1996). Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. *Neurology*, Vol. 47, pp. 160-166.
- Jankovic, J. (2004). Botulinum toxin in clinical practice. *J Neurol Neurosurg Psychiatry*, Vol 7, pp. 951-957
- Kalsi, V.; Apostolidis, A.; Gonzales, G.; Elneil, S.; Dasgupta, P. & Fowler, C.J. (2008). Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. *Eur Urol*, Vol. 54, pp. 181-187.
- Karsenty, G.; Reitz, A.; Lindemann, G.; Boy, S. & Schurch, B. (2006). Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. *Urology*, Vol. 68, pp. 1193-1197.
- Kay, G.G. & Ebinger, U. (2008). Preserving cognitive function for patients with overactive bladder: evidence for a differential effect with darifenacin. *Int J Clin Pract*, Vol 62, pp. 1792-1800.
- Kulaksizoglu, H. & Parman, Y. (2010). Use of botulinum toxin-A for the treatment of overactive bladder symptoms in patients with Parkinson's disease. *Parkinsonism Relat Disord*, Vol. 16, pp. 531-534.
- Lang, A.E. & Obeso, J.A. (2004). Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol*, Vol 3, pp. 309-316.
- Lemack, G.E.; Dewey, R.B.; Roehrborn, C.G.; O'Suilleabhain, P.E. & Zimmern, P.E. (2000). Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. *Urology*, Vol. 56, pp. 250-254.
- Maggi, C.A.; Furio, M.; Santicoli, P.; Conte, B. & Meli, A. (1987). Spinal and supraspinal components of GABAergic inhibition of the micturition reflex in rats. *J Pharmacol Exp Ther*, Vol 240, pp. 998-1005.
- Malcangio, M. & Bowery, N.G. (1996). GABA and its receptors in the spinal cord. *Trends Pharmacol Sci* 17:457-462.
- Mathias, C.J. (2002). Neurodegeneration, parkinsonian syndromes and autonomic failure. *Auton Neurosci*, Vol. 96, pp. 50-58.
- Matsuura, S.; Kakizaki, H.; Mitsui, T.; Shiga, T.; Tamaki, N. & Koyanagi, T. (2002). Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. *J Urol*, Vol. 168, pp. 2035-2039.
- Mehnert, U.; Birzele, J.; Reuter, K. & Schurch, B. (2010). The effect of botulinum toxin type A on overactive bladder symptoms in patients with multiple sclerosis: a pilot study. *J Urol*, Vol 184, pp. 1011-1016.

- Nour, S.; Svarer, C.; Kristensen, J.K.; Paulson, O.B. & Law, I. (2000). Cerebral activation during micturition in normal men. *Brain*, Vol 123, pp. 781-789
- O'Donnell, P.D. (1990). Central actions of bethanechol on the urinary bladder in dogs. *J Urol*, Vol 143, pp. 634-637.
- Pavlakakis, A.J.; Siroky, M.B.; Goldstein, I. & Krane, R.J. (1983). Neurourologic findings in Parkinson's disease. *J Urol*, Vol. 129, pp. 80-83.
- Pehrson, R.; Lehmann, A. & Andersson, K.E. (2002) Effects of gamma-aminobutyrate B receptor modulation on normal micturition and oxyhemoglobin induced detrusor overactivity in female rats. *J Urol*, Vol.168, pp. 2700-2705.
- Pfeiffer, R.F. (2003). Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol*, Vol. 2, pp.107-116.
- Popat, R.; Apostolidis, A.; Kalsi, V.; Gonzales, G.; Fowler, C.J. & Dasgupta, P. (2005). A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. *J Urol*, Vol.174, pp.984-988.
- Porter, R.W. & Bors, E. (1971) Neurogenic bladder in parkinsonism: effect of thalamotomy. *J Neurosurg*, Vol. 34, pp. 27-32.
- Rapp, D.E.; Lucioni, A.; Katz, E.E.; O'Connor, R.C.; Gerber, G.S. & Bales, G.T. (2004). Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. *Urology*, Vol 63, pp. 1071-1075.
- Reitz, A.; Stöhrer, M.; Kramer, G.; Del Popolo, G.; Chartier-Kastler, E.; Panneck, J.; Burgdörfer, H.; Göcking K.; Madersbacher, H.; Schumacher, S.; Richter, R.; von Tobel, J. & Schurch, B. (2004). European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol*, Vol. 45, pp.510-515.
- Reitz, A.; Denys, P.; Fermanian, C.; Schurch, B.; Comperat, E. & Chartier-Kastler, E. (2007). Do repeat intradetrusor botulinum toxin type A injections yield valuable results? Clinical and urodynamic results after five injections in patients with neurogenic detrusor overactivity. *Eur Urol*, Vol. 52, pp. 1729-35.
- Rojo, A.; Aguilar, M.; Garolera, M.T.; Cubo, E.; Navas, I. & Quintana, S. (2003). Depression in Parkinson's disease: clinical correlates and outcome. *Parkinsonism Relat Disord*, Vol. 10, pp. 23-28.
- Rosales, R.L. & Dressler, D. (2010). On muscle spindles, dystonia and botulinum toxin. *Eur J Neurol*, Vol. 17, pp. 71-80.
- Sahai, A.; Dowson, C.; Khan, M.S. & Dasgupta, P. (2009). Improvement in quality of life after botulinum toxin-A injections for idiopathic detrusor overactivity: results from a randomized double-blind placebo-controlled trial. *BJU Int*, Vol. 103, pp. 1509-1515.
- Sakakibara, R.; Shinotoh, H.; Uchiyama, T.; Yoshiyama, M.; Hattori, T. & Yamanishi, T. (2001). SPECT imaging of the dopamine transporter with [(123)I]-beta-CIT reveals marked decline of nigrostriatal dopaminergic function in Parkinson's disease with urinary dysfunction. *J Neurol Sci*, Vol 187, pp. 55-59.
- Sakakibara, R.; Shinotoh, H.; Uchiyama, T.; Sakuma, M.; Kashiwado, M.; Yoshiyama, M. & Hattori, T. (2001). Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. *Auton Neurosci*, Vol. 92, pp. 76-85.

- Schiavo, G.; Rossetto, O.; Benfenati, F.; Poulain, B. & Montecucco, C. (1994). Tetanus and botulinum neurotoxins are zinc proteases specific for components of the neuroexocytosis apparatus. *Ann NY Acad Sci*, Vol. 710, pp. 65-75.
- Schurch, B.; Stohrer, M.; Kramer, G.; Schmid, D.M.; Gaul, G. & Hauri, D. (2000). Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol*, Vol. 164, pp. 692-697.
- Schurch, B.; de Sèze, M.; Denys, P.; Chartier-Kastler, E.; Haab, F.; Everaert, K.; Plante, P.; Perrouin-Verbe, B.; Kumar, C.; Fraczek, S. & Brin, M.F. (2005). Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-mo study. *J Urol*, Vol. 174, pp. 196-200.
- Schmid, D.M.; Sauermann, P.; Werner, M.; Schuessler, B.; Blick, N.; Muentener, M.; Strebel, R.T.; Perucchini, D.; Scheiner, D.; Schaer, G.; John, H.; Reitz, A.; Hauri, D. & Schurch, B. (2006). Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol*, Vol 176, pp. 177-185.
- Seki, S.; Igawa, Y.; Kaidoh, K.; Ishizuka, O.; Nishizawa, O. & Andersson, K.E. (2001). Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. *Neurourol Urodyn*, Vol. 20, pp.105-113.
- Senard, J.M.; Rai, S.; Lapeyre-Mestre, M.; Brefel, C.; Rascol, O.; Rascol, A. & Montastruc, J.L. (1997). Prevalence of orthostatic hypotension in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, Vol 63, pp. 584-589.
- Sille' n, U.; Rubenson, A. & Hja'lmås, K. (1981). On the localization and mediation of the centrally induced hyperactive urinary bladder response to L-dopa in the rat. *Acta Physiol Scand*, Vol 112, pp. 137-140
- Spira, P.J.; Sharpe, D.M.; Halliday, G.; Cavanagh, J. & Nicholson, G.A. (2001). Clinical and pathological features of a parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. *Ann Neurol*, Vol. 49, pp. 313-319.
- Stöhrer, M.; Goepel, M.; Kondo, A.; Kramer, G.; Madersbacher, H.; Millard, R.; Rossier, A & Wyndaele, J.J. (1999). The standardization of terminology in neurogenic lower urinary tract dysfunction: with suggestions for diagnostic procedures. International Continence Society Standardization Committee. *Neurourol Urodyn*, Vol 18, pp.139-158.
- Sussman, D. & Garely, A. (2002). Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin*, Vol. 18, pp. 177-184.
- Todorova, A.; Vonderheid-Guth, B. & Dimpfel, W. (2001). Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol*, Vol. 41, pp.636-644.
- Trompetto, C.; Currà, A.; Buccolieri, A.; Suppa, A.; Abbruzzese, A. & Berardelli, A. (2006). Botulinum toxin changes intrafusal feedback in dystonia: a study with the tonic vibration reflex. *Mov Disord*, Vol. 21, pp. 777-782.
- Trompetto, C.; Bove, M.; Avanzino, L.; Francavilla, G.; Berardelli, A. & Abbruzzese G. (2008). Intrafusal effects of botulinum toxin in post-stroke upper limb spasticity. *Eur J Neurol*, Vol 15, pp.367-370.

- Uchiyama, T.; Sakakibara, R.; Hattori, T.; Yamanishi, T. (2003). Short-term effect of a single levodopa dose on micturition disturbance in Parkinson's disease patients with the wearing-off phenomenon. *Mov Disord*, Vol 18, pp. 573-578.
- Wagner, T.H.; Patrick, D.L.; Bavendam, T.G. et al. (1996). Quality of life of persons with urinary incontinence: development of a new measure. *Urology*, Vol 47, pp. 67-71.
- Ward, A.B.; Molenaers, G.; Colosimo, C. & Berardelli, A. (2006). Clinical value of botulinum toxin in neurological indications. *Eur J Neurol*, Vol. 13, Suppl. 4, pp. 20-26.
- Winge, K.; Werdelin, L.M.; Krøyer, K. & Stimpel, H. (2002). Bladder dysfunction in young patients with Parkinson's disease. *Mov Disord*, Vol 17, Suppl. 5, S 218.
- Winge K.; Rasmussen, D.; Werdelin, L.M.(2003). Constipation in neurological diseases. *J Neurol Neurosurg Psychiatry*, Vol 74, pp. 13-19.
- Winge, K.; Werdelin, L.M.; Nielsen, K.K & Stimpel, H. (2004). Effects of dopaminergic treatment on bladder function in Parkinson's disease. *Neurourol Urodyn*, Vol. 23, pp. 689-696.
- Winge, K.; Friberg, L.; Werdelin, L.; Nielsen, K.K. & Stimpel, H. (2005). Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. *Eur J Neurol*, Vol 12, pp. 842- 850
- Winge, K. & Fowler, C.J. (2006). Bladder dysfunction in Parkinsonism: mechanism, prevalence, symptoms and management. *Mov Disord*, Vo 21, pp 737-745.
- Yoshimura, N.; Mizuta, E.; Kuno, S.; Sasa, M.& Yoshida, O. (1993). The dopamine D1 receptor agonist SKF 38393 suppresses detrusor hyperreflexia in the monkey with parkinsonism induced by 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Neuropharmacology*, Vol 32, pp. 315-321.
- Yoshimura, N. ; Mizuta, E. ; Yoshida, O. & Kuno, S. (1998). Therapeutic effects of dopamine D1/D2 receptor agonists on detrusor hyperreflexia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys. *J Pharmacol Exp Ther*, Vol 286, pp. 228-233.
- Yoshimura, N. (1999). Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder. *Prog Neurobiol*, Vol. 57, pp. 583-606.
- Yoshimura, N.; Kuno, S.; Chancellor, M.B.; de Groat, W.C. & Seki, S. (2003). Dopaminergic mechanisms underlying bladder hyperactivity in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway. *Br J Pharmacol*, Vol 139, pp. 1425-1432.



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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of α -synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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